Influence of new treatment modalities on adherence in glaucoma

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Abstract: PURPOSE OF REVIEW It is well known that glaucoma patients are not adherent to their therapeutic regimens. The issue of nonadherence is multifactorial and includes inadequate communication between doctors and patients, resulting in significant costs associated with enhanced disease progression. Therapeutic regimens are risk factors which often influences adherence rates. Thus, alternative treatment modalities, especially those risk factors that do not rely on patients' cooperation, may enable improvements in long-term outcomes of glaucoma in patient. RECENT FINDINGS The studies selected for this review were divided into new medications, especially advancements in pharmaceutical approaches to treat glaucoma and new ways of delivering the medication, new surgical methods, especially minimally invasive surgery methods for glaucoma, and new studies about adherence in glaucoma. SUMMARY Surprisingly, a very few studies on glaucoma medication or surgery addressed the concept of adherence. However, adherence is discussed in studies which consider psychological aspects of patients or communication issues between doctors and patients. Although these studies were performed in clinical settings, the issue of adherence is not addressed; despite it has significant effect on long-term outpatient care. A combination of both aspects, adherence and miscommunication, should be considered in studies.

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Recent findings
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Summary
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Keywords
adherence, glaucoma diagnostic, glaucoma therapy

OUTLINE/INTRODUCTION

The rising prevalence of glaucoma worldwide invites not only awareness of limitations in current therapies but also advancements in the therapeutic options to better enable adequate treatment to this increasing population. According to the European Glaucoma Society guidelines (2014), glaucoma therapy should be easy to use, have few side-effects, and be cost effective. It is well known that adherence is one of the defining factors of effective glaucoma management regimes and that glaucoma has low adherence and low persistence rates. Several factors influence the adherence rate of patients. Tsai [1] systematically studied obstacles to medication adherence and found situational and environmental factors, medication regimens, and patient's and provider's factors influencing adherence. Insufficient communication between doctors and patients causes frequent changes in therapeutic regimens. Patients have better adherence immediately before their consultations which leads to a false impression of ''adequate'' intraocular pressure (IOP) control. Subsequent progression of visual fields and optic nerve disc changes, however, would seem to lack explanation. Hence, nonadherence leads to disease progression and associated higher costs [2]. With the importance of therapeutic regimens to which patients adhere, or regimens which require less patient involvement, in mind, the question arises as to how new therapeutic modalities (new medicines, new ways of application, and new surgical options) might influence

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KEY POINTS

- Adherence and persistence rates in the treatment of glaucoma are relatively low compared to other chronic diseases. Continuous patient education and checks for glaucoma progression are mandatory requirements in disease management.
- Significant inconsistency in the study design of MIGS trials confounds information presented.
- We suggest as a minimal requirement for surgical studies: wash out IOP at baseline and at the end of the study with a minimum 2 years of follow-up. In addition, a consensus on how to define success is needed.

adherence rates and ultimately disease management. The goal of this review is to provide an overview of the recent literature on new therapeutic approaches in glaucoma and their influence on patient adherence.

MATERIAL AND METHODS

Three aspects have been reviewed: new pharmaceutical approaches; new surgical approaches, minimally invasive surgery (MIGS) and others; and new studies addressing adherence in glaucoma. A PubMed literature research was conducted. Included in this review are manuscripts which have been published between 1 July 2017 and 31 August 2018 with the search strings: 'glaucoma, adherence, MIGS, minimally invasive glaucoma surgery, medication, treatment, rhokinase inhibitors (ROCK), and NO donor'. Only original peer-reviewed articles in English where included. In addition, a few reviews of major interest where added.

RESULTS

New pharmaceutical approaches to treat glaucoma and new ways of delivering medication

It is well known that the IOP depends mainly on the physiological circulation of the aqueous humor. Therefore, the two important therapeutic approaches to reduce IOP are a reduction of aqueous humor production or an enhancement of aqueous humor outflow. Most of the aqueous humor exits the eye through the trabecular or 'conventional' outflow system, in contrast to the uveoscleral or 'unconventional' pathway.

The main site of outflow resistance which leads to an elevation of IOP is within the juxtacanalicular portion of the trabecular meshwork and the inner wall of Schlemm's canal. In 2017, the first drugs acting directly on trabecular meshwork, ROCK, were launched: netarsudil has a triple action; it inhibits the Rhokinase pathway, inhibits the norephedrine pathway and enhances outflow by lowering the episcleral venous pressure [3,4]. Several studies considered the efficacy of ROCK. Chihara [5] and Ohta [6] showed that Ripasudil not only lowered IOP but also increased ocular blood flow and the density of peripapillary vessels. Netarsudil and another ROCK, fasudil, enabled an IOP reduction in the range of timolol (slightly less than prostaglandin analogues), which was ongoing for a longer time. The only side-effect was hyperemia [7,8]. Studies combining ROCK with prostaglandin agonists are ongoing. A study looking at the IOP-lowering effect of ripasudil in uveitic glaucoma found an IOP reduction of 5 mm of a median of 23 mm, but only 50% of their patients responded to this drug [9].

A novel prostaglandin agonist which donates nitric oxide while metabolizing was also recently launched. Latanoprostene bunod metabolizes to latanoprost acid (increasing uveoscleral outflow) and butanediol mononitrate (increasing conventional outflow by direct action of the released NO at the trabecular meshwork) [10].

Other pharmacologic agents treat fibrosis at the level of lamina cribrosa as a potential target site to lower IOP and also target fibrosis at the conjunctiva as a potential treatment for preventing post filtering surgery fibrosis [11,12]. An interesting new approach was described by Ohia [13] and Patil [14]. H_2S, a gaseous transmitter can relax contracted vascular smooth muscles in several parts of the body including the eye and might be a potential drug for lowering IOP [13,14]. Other potentially IOP lowering drugs (adenosine receptor agents and small interfering RNAs) are currently being studied [15,16].

Often discussed is the action of cannabis on IOP, especially after recent legalization of this drug in many countries, Bowen showed that smoked cannabis clearly reduced IOP (up to 6.6 mmHg), but the effect lasted only up to 4 h [17]. This dosing requirement in addition to other well-known side-effects has prevented cannabis in its current form from becoming a treatment of choice for glaucoma. Chinese herbal medicine for the treatment of primary open-angle glaucoma is yet another interesting option pending an examination of evidence-based practice guidelines [18]. Traditional Chinese medicine focuses on the patient's entire body rather than targeting specific organs. In treating glaucoma with traditional Chinese medicine, blood circulation, not IOP is the main focus.

Chronic application of antiglaucomatous drops, especially if they contain preservative agents, leads to changes and subsequently often damage to the

ocular surface [19]. Kim [20] showed that glaucoma patient using topical medications had a higher incidence of Meibomian gland disease than controls. One of the main problems of any ongoing application of preservative agents is an inflammatory response with symptoms of burning, photophobia, and foreign body sensation. A new drug, topical palmitoylethanolamide, showed in a study by Di Zazzo [21] a significant improvement of the topical surface parameters. The common method of applying antiglaucomatous medication is via topical eye drops which often contain preservative agents, hence in recent years, preservative-free eye drops, which have less effect on the ocular surface, have replaced many conventional drops.

Other means of application, which rely on less patient adherence, would be preferable, because we know that glaucoma patients are especially not very successful in applying drops [22]. Another alternative way of delivering a drug is via microspheres, a method which has been examined by Tian *et al.* [23]. These microspheres' goal is to prolong the duration of action of the drugs, thus enabling less frequent use.

New Surgical Approaches to Treat Glaucoma, Minimally Invasive Glaucoma Surgery Procedures

Multiple studies on MIGS procedures have been published within the last year. The majority focus on procedures that enhance conventional, trabecular outflow. There have also been a number of publications on the fistulating XEN procedure in which an ab interno implant conducts aqueous humor from the anterior chamber to the subconjunctival space. In addition, there are three publications describing novel ultrasound-based cyclodestructive procedure.

iStent Trabecular Micro-bypass Stent

In a retrospective study, Buffet *et al.* [24] evaluated the 24-month outcome of 63 eyes of 41 patients after combined phaco and implantation of two iStents (Glaukos Corporation, San Clemente, California, USA) in mild to advanced chronic open-angle glaucoma. IOP dropped from 16.8 ± 3.0 mmHg on 2.3 ± 0.9 medications by 10% at 2 years [24]. At the same time medications were reduced by 40% [24]. No severe device-related adverse events were noted [24]. A minimal hyphema occurred in 3% of the patients which resolved in the first week [24].

XEN45 Gel Stent

Widder *et al.* followed-up 261 eyes after XEN45 Gel Stent (Allergan plc, Irvine, California, USA) implantation for 8.5 months [25▪]. IOP was lowered from 24.3 mmHg (SD 6.6) to 16.8 mmHg (SD 7.6), and the hypotensive medications were reduced from 2.6 (SD 1.1) to 0.2 (SD 0.7) [25▪]. Needling rate was not neglectable with 34%. The group found a higher success rate in pseudophakic eyes, compared to combined surgery or surgery in phakic eyes [25▪]. Hohberger *et al.* [26] found a success rate of 47% in XEN Gel stent alone ($n = 81$) compared to 53% in combined XEN and phaco ($n = 30$) with 6 months of follow-up. Success was defined as IOP less than 18 mmHg without local antiglaucomatous therapy or further surgical interventions [26]. In a singlearm, open-label, multicenter clinical study, Grover *et al.* followed 65 eyes for 12 months [27]. All eyes were treated with mitomycin. Success was achieved in 75% of the cases defined as percentage of eyes achieving more than 20% IOP reduction from baseline on the same or fewer medications at month 12 [27]. To achieve this goal, a needling was required in 32.3% of the patients (9.2% had two needlings and 2% had three needlings) [27]. Mean IOP reduction from baseline was 9.1 mmHg and number of medications was reduced from 3.5 to 1.7 [27]. De Gregorio *et al.* [28] published a nonrandomized, prospective study of 41 eyes of 33 patients of combined phaco and XEN45 Gel Stent implantation. Complete success rate was 80% defined as a postoperative IOP more than 6 and less than 17 mmHg without glaucoma medications [28]. IOP was 22.5 ± 3.7 mmHg on 2.5 ± 0.9 medication classes at baseline and was reduced at 12 months to 13.1 ± 2.4 mmHg (-42%) on 0.4 ± 0.8 medication classes [28].

Microhook ab interno trabeculotomy

A retrospective case-series was published of combined phaco and ab interno trabeculotomy with a microhook of 68 eyes of 48 patients in a Japanese population [29]. Mean preoperative IOP decreased from 16.4 ± 2.9 mmHg on 2.4 ± 1.2 antiglaucoma medications to 11.8 ± 4.5 mmHg on 2.1 ± 1.0 mmHg mmHg at 9.5 months postoperatively [29]. Hyphema was the most common postoperative complication [29].

Gonioscopy-assisted Transluminal Trabeculotomy

Rahmatnejad *et al.* [30▪] retrospectively reported outcomes of 66 cases of gonioscopy-assisted transluminal trabeculotomy with an iTrack microcatheter (Ellex iScience Inc., Fremont, California, USA) in open-angle glaucoma. Follow-up ranged from 3 to 30 months with an average of 11.9 months [30▪].

Mean IOP was reduced from 26.1 ± 9.9 mmHg on 3.1 ± 1.1 medications to 14.6 ± 4.7 mmHg on 1.2 ± 0.9 medications at 12 months [30▪]. Success rate (defined as IOP reduction >20% from baseline or IOP between 5 and 21 mmHg, and no need for further glaucoma surgery) was 63% [30▪]. Success rate was higher in Whites (69%) versus Blacks (42%) [30▪]. The main postop complication was hyphema, which was present in 38% of the cases at 1 week and 6% at 1 month [30▪].

Ab interno Trabeculotomy with the Trabectome

Kostanyan *et al.* [31] published a comparison study of 29 matched Baerveldt glaucoma drainage implant cases to 30 cases after ab interno trabeculectomy with the trabectome [31]. The primary outcome measures were IOP, number of glaucoma medications, and a Glaucoma Index score, which reflected glaucoma severity based on visual field, the number of preoperative medications, and preoperative IOP [31]. Success, defined as an IOP less than 21 mmHg, more than 20% reduction, and no reoperation, was achieved in 50% in the ab interno trabeculectomy with the trabectome group versus 52% in the Baerveldt glaucoma drainage implant group at 2.5 years [31]. Both groups had similar IOP after 30 months (15 mmHg) [31].

Ultrasound Cyclo Plasty

Ultrasound cyclo plasty (UCP) is a nonincisional technique to reduce IOP in glaucoma by coagulation of ciliary body (EyeOP1, Eye Tech Care, Rillieux-la-Pape, France) [32]. The procedure is performed in the operating room under peribulbar anesthesia [32]. A 'coupling cone' is placed in contact with the eye (available in three sizes: 11, 12, and 13 mm in diameter) and ultrasound energy is delivered by six piezoelectric transducers focused on the ciliary body [32]. Recently, a multicentre prospective study from Italy with a 1-year follow-up was published [33]. In total, 49 eyes from 47 patients were included [33]. Mean IOP decreased from 27.7 ± 9.2 to 19.8 ± 6.9 mmHg ($P < 0.001$), and the mean number of hypotensive medication decreased from 3.2 to 2.3 simultaneously ($P < 0.05$) [33]. Qualified success rate was 51% and complete success rate was 43% [33]. Criteria of qualified success were IOP reduction to at least 20% and more than 5 mmHg without adjunctive hypotensive medication, whereas complete success was as above and IOP less than 21 mmHg [33]. Prospectively, De Gregorio *et al.* [34] investigated 40 eyes of 40 patients for 1 year with a diagnosis of primary or secondary uncontrolled glaucoma under maximal tolerated medical therapy. Complete success was defined as a final IOP more than 5 mmHg and 21 mmHg or less without hypotensive medication adjunction and no major or vision-threatening complications [34]. A retreatment after 4 months was allowed whenever IOP was more than 21 mmHg [34]. Baseline IOP was 32.5 ± 9.9 mmHg.(43) IOP reduction was 27.8% at 4 months [34]. Retreatment was required in every second eye and 30% of the eyes required three UCP procedures within 1 year [34]. Overall success at 12 months was 85% [34].

DISCUSSION

Few studies have been published on MIGS procedures in the last 12 months. The majority were on the XEN45 Gel stent and UCP. In addition, significant inconsistency in the study design of MIGS trials confounds information presented. As a minimal requirement, the following study design is suggested by the Federal Drug and Food administration: wash out IOP at baseline and at the end of the study and at least 2 years of follow-up. In addition, a consensus on how to define success is needed. Many studies adapted criteria from the tube versus trabeculectomy study, that is, IOP of 21 mmHg or less and IOP reduction more than 20% from baseline [35]. However, we believe a pressure of 21 mmHg or less would not be considered a successful outcome in a clinical setting in most glaucoma patients. Much more strict criteria are needed, for example, IOP of less than or equal to 18 or 16 mmHg to define clinically relevant success. For future studies, we strongly suggest that standardized study designs and outcome criteria are adopted to better enable the evaluation of MIGS procedures and to enable comparisons.

Glaucoma is unique in that adherence and persistence rates in the treatment of glaucoma are relatively low compared to other chronic diseases which require lifelong therapeutic interventions [36]. Self-reported adherence rates tend to be lower than actually measured adherence rates. However, one study tested a wireless monitoring device compared to self-reported activity via a questionnaire [37]. Interestingly, the self-reported median adherence was 82% and dropped after 30 days, but was higher than the objectively measured adherence (56 versus 52.2%). The authors confirmed that the self-reported and the objectively measured adherence rate differed and suggested considering implementation of such a measuring device in daily practice. The question often arises whether or not increasing patient understanding of his or her disease and about their therapy improves adherence. Fiscella

[38▪] looked at over 23 000 patients and found no improvement in adherence despite intensive education by means of mailings. This is understandable considering the study of Anbesse [39] in which the most often cited reasons for nonadherence are: forgetfulness, being busy, and being away from home. It is very important to incorporate a therapeutic program which is easy to use and easy to integrate into the daily lives of patients. Young patients tend to show lower adherence, in spite of having greater access to electronic devices. They manage online information without a doctor's help, but this does not seem to improve their adherence [40]. Knowing that patients with a reduced visual quality of life at the beginning of their disease show a reduced adherence when first measured, we should improve their education about their disease which leads to improved adherence to their therapeutic regimens [41]. An important step to improve adherence is as simple as providing instructions about eye drop instillation techniques [42].

CONCLUSION

Adherence and compliance are still a problem in management of chronic diseases as glaucoma. Thus, continuous education of patients is crucial to improve adherence and compliance.

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Conflicts of interest

There are no conflicts of interest.

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